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RESEARCH ARTICLE

Development and Characterization of Ranitidine Hydrochloride Mucoadhesive Hydrogel Beads

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Abstract

Objectives: To formulate mucoadhesive hydrogel beads of Ranitidine hydrochloride for site-specific drug delivery in the stomach. The site-specific delivery was acquired by using mucoadhesive polymers in formulation development. **Methods:** The best method used for the preparation of mucoadhesive hydrogel beads was the ionic gelation method. For the achievement of mucoadhesive and controlled release properties of the formulation ionic gelation method used by varying concentrations of polymers. **Findings:** Pre-fomulation parameters were studied before the development of formulation such as melting point, and FTIR studies. Post-formulation evaluation parameters studied were drug content, invitro mucoadhesion test, swelling index, water uptake studies, SEM analytical studies, and invitro drug release studies. Nine formulations showed good swelling index, water uptake studies, and drug content. The SEM results revealed that beads maintained good surface morphology with a spherical shape. Mucoadherence was in the range of 66% to 77%. The optimized formulation was found with drug release up to 14hrs with 98.9% of drug release. **Novelty:** Mucoadhesive hydrogel beads of Ranitidine hydrochloride were developed by using primary polymer sodium alginate to acquire mucoadhesive properties and site-specific application. Other secondary polymers such as sodium carboxy methylcellulose, hydroxy propyl methyl cellulose, and Carbopol contribute to the controlled release of drugs from hydrogel beads.

Keywords: Hydrogel beads; Ranitidine HCl; Sodium alginate; Ionotropic gelation; Mucoadhesion

1 Introduction

Hydrophilic polymer networks that form a three-dimensional structure are referred to as hydrogels[(1)]. The three-dimensional polymeric network for hydrogels was provided by chemical and/or physical crosslinks in spite of swelling[(2)]. The swelling ability of hydrogels is provided by the presence of hydrophilic functional groups in the

presence of water without dissolving [3]. Various polymers are used in the formulation of hydrogels they are natural and synthetic polymers [4]. These hydrogels have a wide range of applications in the biomedical and pharmaceutical sectors [5]. Polymer density, elasticity, and breakdown rate were provided by changes in crosslinking density and composition of polymers in the formulation of hydrogels [6]. Hydrogels provide the most significant attributes that drive them outstanding usage in pharmaceutical applications majorly in the field of drug delivery systems. The main advantage related to hydrogels is that gel formation proceeds at ambient temperature and rarely requires organic solvents for preparation [7]. Hydrogels provide biodegradability, biocompatibility, and excellent drug encapsulation efficiency [8]. Various methods specified for the preparation of hydrogels are Isostatic ultra-high pressure, Use of cross linkers, nucleophilic substitution reaction method, use of gelling agents, irradiation, and freeze-thawing method [9]. Hydrogels have swelling ability in the presence of water and the drug is entrapped into pores of hydrogels by imparting mechanical strength to the polymers, cross linkers are used in hydrogel preparation [10]. The crosslinkers used in hydrogel preparation are calcium chloride, glutaraldehyde, and oxidized konjac glucomannan (DAK) [11]. Crosslinking is provided by two ways physical and chemical crosslinking methods. Crosslinkers have the ability to control the burst release of drugs from polymer networks [12]. Ranitidine is a selective H2 receptor antagonist that inhibits acid production by binding to H2 receptors on the basolateral membrane of parietal cell therapy in most cases [13]. Ranitidine is a widely used drug for reducing gastric acid secretion in the human body [14]. Controlled release and Site-specific release of ranitidine in stomach is provided by development of mucoadhesive hydrogel beads using bio-adhesive polymers [15].

2 Methodology

Ranitidine HCl, Drugs India, HYD. Sodium alginate, Finar Chemicals Ltd. Carbopol, Sodium Carboxy Methyl Cellulose, Calcium chloride, Hydrochloric acid, Sodium hydroxide pellets from SD fine chemicals, Mumbai. Hydroxy Propyl Methyl Cellulose - K100 from top pharmaceuticals Bangalore. Potassium dihydrogen phosphate, Disodium hydrogen phosphate, Qualigens fine chemicals.

2.1 Pre formulation Studies

2.1.1 Calibration curve was constructed at pH 7 4 phosphate buffer

A weighed amount (100mg) of Ranitidine hydrochloride was dissolved in Phosphate buffer [16]. (pH7.4) and make volume up to 100 ml (Stock solution I, 1000 μg/ml). Pippete out 10 ml of stock solution and make up the volume up to 100 ml (Stock solution II, 100 μg/ml). Aliquots of the required concentration from 30 to 300 μg/ml were prepared from the stock solution II, and the absorbance was measured at 313 nm against the reagent blank.

Table 1. Standard curve data at pH 7.4 phosphate buffer

Concentration in μg/ml	Absorbance at 313 nm
0	0
30	0.132
60	0.198
90	0.256
120	0.348
150	0.465
180	0.546
210	0.635
140	0.748
270	0.832
300	0.993

2.2 Formulation Studies

2.2.1 Preparation of Hydrogels Without Drug

The ionotropic gelation approach was used to physically crosslink the hydrogels. Sodium alginate, HPMC-K100, Carbopol, and SCMC, were weighed precisely and then dissolved in the necessary amount of distilled water. The solution was homogenized for 30 minutes at 500 rpm. After sonicated for 30 minutes to eliminate air bubbles, this solution was injected with a 21G syringe into

a 2% $Cacl_2$ solution (the crosslinking agent), where it was allowed to form hydrogels for 30 minutes [17]. The formed hydrogels were cleaned with distilled water before drying at room temperature.

2.2.2 Formulation of Ranitidine HCl Hydrogels

A physical crosslinking (ionic gelation method) approach, was used to create the hydrogels. Sodium alginate, SCMC, HPMC K100, Carbopol and ranitidine HCl, ingredients were weighed as shown in the Table 2 and dissolved in the necessary amount of distilled water, and the resulting solution is being homogenized for 30 minutes at 500 rpm. To get rid of air bubbles, the homogenized solution was sonicated for 30 minutes. For the development of hydrogels, the solution was dropped into a 2% $Cacl_2$ (crosslinking agent) solution using a 21G syringe. The developed hydrogels were cleaned with distilled water before being drying at room temperature.

Table 2. Compositions of Ranitidine HCl hydrogel beads formulation

Formulation code	Drug (% w/v)	Polymers			
		Sodium alginate (% w/v)	SCMC (% w/v)	Carbopol (% w/v)	HPMC K100 (% w/v)
R1	1	2	1	-	-
R2	1	2	2	-	-
R3	1	2	3	-	-
R4	1	2	-	1	-
R5	1	2	-	2	-
R6	1	2	-	3	-
R7	1	2	-	-	1
R8	1	2	-	-	2
R9	1	2	-	-	3

3 Physicochemical Evaluation

3.1 FTIR Studies

Studies on the compatibility of drugs and polymers were conducted by Fourier transform infrared (FTIR) spectroscopy. To confirm that drug entrapment within polymeric systems involves a physical mechanism and no chemical interaction between drug and polymers. Since there was no discernible interaction between the FTIR spectra of the pure drug, individual polymers, and the combination, the drug and polymers were chosen as being well-suited for the creation of hydrogel beads.

3.2 Drug Entrapment Efficiency

Using a mortar and pestle, dried beads with 100 mg equivalent weight were triturated. The triturated hydrogels were transferred into volumetric flask which was filled with pH 7.4 phosphate buffer solution and left to stand for 24 hours. These hydrogel beads underwent appropriate dilutions and filtering at predetermined intervals before the absorbance was measured spectrophotometrically at 313 nm.

3.3 In-Vitro Mucoadhesion Test

The in vitro wash-off test was used to conduct the in vitro mucoadhesion test. On a strip of goat intestine that was attached to a glass slide using cyanoacrylate adhesive, 100 hydrogel particles were counted and deposited. Then, an eight-hour disintegration process was performed on this particle-filled slide. After eight hours, the number of attached particles was counted, and the percentage of adhesion was calculated.

3.4 Swelling index

The gravimetric approach was used in triplicate to measure the swelling of hydrogels. Hydrogels of a known weight were added to pH 7.4 phosphate buffer solution and heated to 37°C. At predetermined intervals after that, the hydrogels were taken out, wiped with tissue paper to eliminate excess solvent, and then immediately weighed. The amount of pH 7.4 phosphate buffer

solution absorbed by hydrogels after specific time intervals (60 min) has been determined by the difference in weight[18].

3.5 In-Vitro Drug Release Studies

With the aid of the USP dissolving test apparatus (paddle method), research on the in vitro drug release of ranitidine HCl was carried out. The USP dissolving device was swirled at a velocity of 50 rpm and thermostatic at a temperature of 37°C. For the first two hours, 100 mg ranitidine HCl equivalent hydrogel beads from each formulation were placed in 900 ml of pH 1.2 HCl buffer. Then 900 ml of new pH 7.4 phosphate buffer is added to the acidic buffer to approximate the pH of the stomach and intestines. To keep the sink condition throughout the trial, 5 ml aliquots were taken out at hourly intervals and refilled with an equivalent volume of dissolving media. After an appropriate dilution, the samples were filtered and subjected to a spectrophotometric analysis at 313 nm. Calculations were used to determine the total drug release.

3.6 Water uptake

A known weight of hydrogels was collected and submerged at 37°C in an excess of distilled water. Subsequently, the hydrogels were taken out at specific intervals, instantly weighed, and the excess solvent was wiped away using tissue paper. The amount of water absorbed by hydrogels for a specific amount of time has been determined by the weight difference[19].

3.7 SEM analysis

The surface morphological studies and shape of the dried hydrogels were examined by using scanning electron microscopy.

4 Results and Discussion

Ranitidine HCl hydrogels were created utilizing the ionotropic gelation process, a physical cross-linking approach, and a variety of polymers, including sodium alginate, HPMC K100, SCMC, and carbopol. A crosslinking agent is included in the solvent, which is composed of distilled water and 2% $CaCl_2$. The physical-chemical characteristics of the synthesized hydrogels, such as swelling ratio, water absorption, percentage yield, drug entrapment efficiency, and size analysis were evaluated.

4.1 Preformulation studies by FTIR

The FTIR spectra of Ranitidine HCl, Sodium Alginate SCMC, HPMC, CP, and the combination of drug and polymers showed no significant interaction between drug and polymer. The FTIR spectra of Ranitidine HCl, Sodium Alginate, SCMC, HPMC, Carbopol, and a mixture of the drugs along with polymers are shown in Figures 1, 2, 3, 4, 5 and 6.

The physicochemical compatibility of the drug and the polymer was established through FTIR studies. IR spectral analysis of Ranitidine HCl showed the peaks at wave numbers of 3256.27, 3191.01 (Associated N-H Stretching), 3101.00 (CH Asymmetric Stretching), 2945.11, 2558.80, 2509.32, 2466.15 (Ring Stretching), 1568.60 (NO_2 Asymmetric Stretching), 1226.15, 1190.50, 1128.81, 1072.07, 1042.61 (C-N Stretching), 803.74, 759.45, 697.73 (N-H Bending out of plane) 759.45, 697.73 (C-S Stretching) confirming the purity of drug with standard respectively.

Table 3. Physical evaluation parameters for Mucoadhesive hydrogel beads

Formulation code	% Yield	Drug content (mg)	Drug entrapment efficiency	Gel fraction	Size analysis	
					Dried beads	Wet beads
R1	94.6±1.52	82± 0.03	85.6± 0.57	98.4±0.1	1.20±0 .32	2.30±0.01
R2	94.3±1.53	86± 0.01	87± 1	99.3±0.1	1.38 ±0.12	2.43±0 .12
R3	93.3±1.15	91.2±0.03	92.7± 1.15	99.56±0.05	1.48± 0.02	2.66±0 .32
R4	95.6±2.08	90.1± 0.03	91.6± 1.52	98±0.1	1.20 ±0.11	2.32±0 .17
R5	95.6±1.52	85± 0.01	85.6± 1.15	98.43±0.15	1.50±0 .14	2.40± 0.51
R6	94.6±0.5	90.4± 0.04	91± 1	98.6±0.1	1.65± .051	2.51± 0.21
R7	92.3±1.15	91.3 ±0.05	92.6± 1.52	99.1±0.1	1.28 ±0.05	2.41± 0.09
R8	92±1	88.7± 0.23	89.6± 1.15	99.56±0.01	1.65±0 .04	2.52± 0.02
R9	98±0.57	94.3± 0.03	95± 1	99.83±0.05	1.83±0 .04	2.93± 0.19

IR spectral analysis of showed the peaks at wave numbers in the physical mixture of Ranitidine HCl with sodium alginate, SCMC, HPMC, CP the major peaks of Ranitidine HCl 3258.73, 3193.75 (Associated N-H Stretching), 3103.94 (CH Asymmetric Stretching), 2944.84, 2560.78, 2511.30 and 2469.05 (Ring Stretching). 1570.17 (NO2 Asymmetric Stretching), 1222.45, 1192.92,

1131.40, 1072.30, 1045.07 (C-N Stretching), 802.96, 760.46, 698.45 (N-H Bending out of plane), 760.46, 698.45 (C-S Stretching), 3259.380 (Associated N-H Stretching), 3108.73 (CH Asymmetric Stretching), 2559.67, 2512.56, 2467.58 (Ring Stretching), 1572.54 (NO_2 Asymmetric Stretching), 1223.74, 1192.26, 1130.35, 1070.83, 1045.47 (C-N Stretching), 803.57, 759.97, 698.04 (N-H Bending out of plane), 759.97, 698.04 (C-S Stretching) wave numbers. However, other peaks were absorbed in physical mixes, which may have been caused by the presence of polymers and showed that ranitidine HCl and other excipients did not interact chemically.

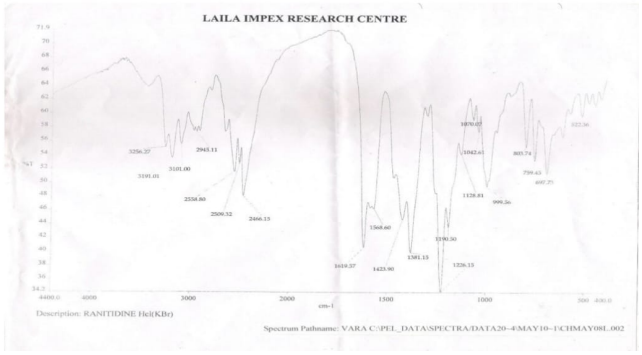

Fig 1. FTIR Spectra of Ranitidine HCL

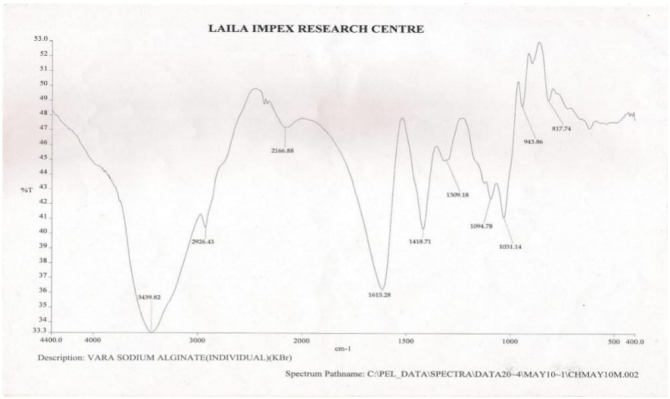

Fig 2. FTIR Spectra of Sodium Alginate

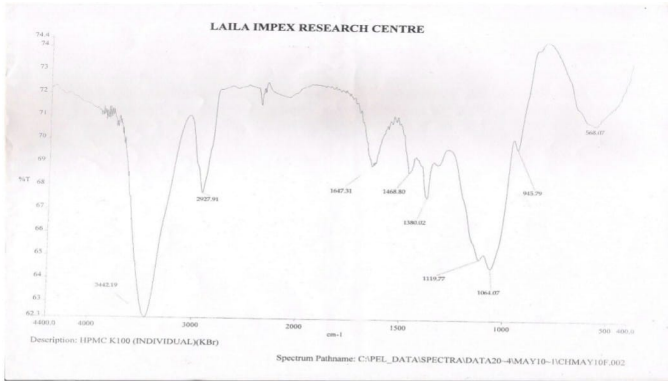

Fig 3. FTIR Spectra of HPMC K100

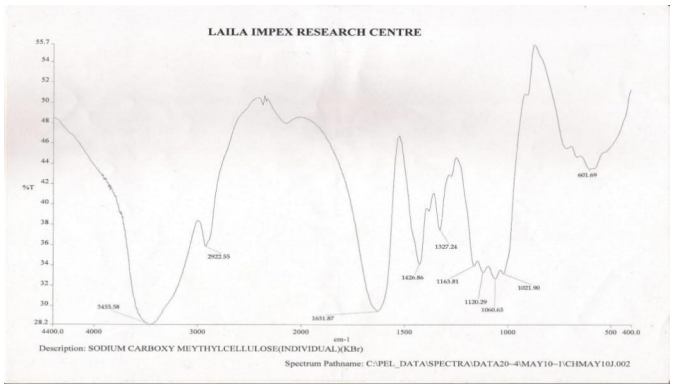

Fig 4. FTIR Spectra of Sodium Carboxy Methyl Cellulose

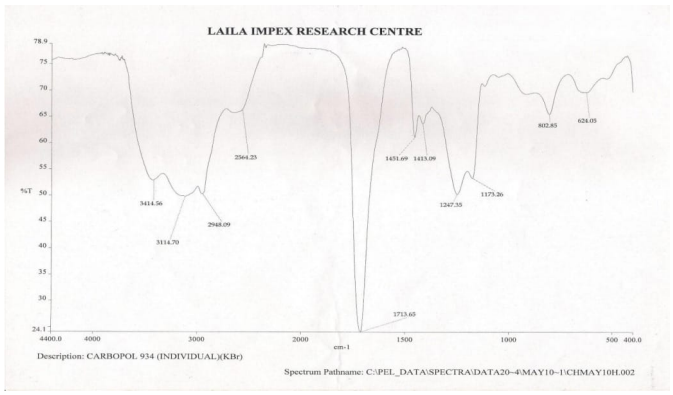

Fig 5. IR Spectra of Carbopol 934

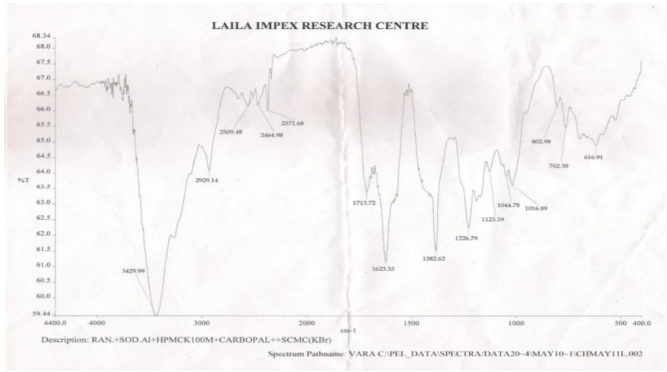

Fig 6. FTIR Spectra of Ranitidine HCL, Sodium Alginate, Carbopol, HPMC K100, and SCMC

4.2 Drug entrapment efficiency

Drug entrapment efficiency mainly gives the amount of drug entrapped in the formulation. The drug entrapment efficiency was in the range of 82.1± 0.03 to 94.3±0.03%. The drug entrapment efficiency for floating micro balloons was in the range of 63 to 70% when HPMC K4M was alone used with various concentrations, an increased concentration of gelling polymer led to the increased percentage of encapsulation efficiency of around 70% [20]. But in comparison to the present research work due to the combination of gelling polymers, the entrapment efficiency is increased in the range of 82 to 94%.

4.3 In-vitro Mucoadhesion test

The in-vitro mucoadhesion test was performed by using the in vitro Wash- Off test. The % Adherence was in the range of 62 % to 77 %. After 12 hours of an invitro mucoadhesion test, the percentage of mucoadhesion for microspheres was in the range of 50 to 60%, which indicated a gradual increase in the gelling agent's concentration contributed to mucoadhesion of microspheres[21]. In the present research work the percentage of mucoadhesion was between 62 to 77% where sodium alginate along with other gelling polymers combination have provided good mucoadhesion properties when compared to other polymers.

Table 4. In-vitro mucoadhesion test

Formulation code	% Adherence
R1	72 %
R2	74%
R3	75%
R4	62%
R5	63%
R6	66%
R7	73%
R8	74%
R9	77%

4.4 Swelling ratio

Swelling studies was done in triplicate using phosphate buffer. The prepared Ranitidine HCl hydrogels showed good swelling properties. The observed swelling ratio for formulations R1, R2, R3, R4, R5, R6, R7, R8, R9 are as follows 7.6± 0.05, 8.2 ±0.05, 10.7± 0.05, 6.6± 0.05, 7.3± 0.11, 9.6± 0.05, 9.6±0.05, 10.6± 0.05, 12.6± 0.05 respectively. Swelling behaviour of drug loaded AvT-co-poly hydrogel investigated research results had revealed with minimum swelling index pH 1.2[22] when compared to present research work. According to the findings, the formulations demonstrated the necessary excellent swelling ratio for hydrogels, which may have an impact on the drug release as well as the mucoadhesive nature of hydrogels.

Table 5. Swelling ratio data for all formulations

Formulation code	Time in mins					
	60	**120**	**180**	**240**	**300**	**360**
R1	1.2±0.05	2.6± 0.1	4.5 ±0.1	5.4± 0.15	7.2± 0.05	7.6± 0.05
R2	2.2± 0.05	3.6 ±0.05	4.4 ±0.05	6.4± 0.05	7.3± 0.05	8.2 ±0.05
R3	2.7± 0.11	4.3± 0.05	6.2± 0.11	7.5± 0.1	10.7± 0.05	10.7± 0.05
R4	0.5± 0.15	2.6± 0.15	3.6± 0.05	4.3± 0.05	6.6± 0.05	6.6± 0.05
R5	1.3± 0.1	3.4± 0.15	4.7± 0.05	5.4± 0.05	7.3± 0.11	7.3± 0.11
R6	1.7 ±0.1	4.6± 0.1	6.5± 0.15	7.5± 0.05	9.6± 0.05	9.6± 0.05
R7	1.0±0.1	2.6± 0.1	5.3 ±0.11	9.4± 0.05	9.6 ±0.05	9.6±0.05
R8	1.6 ±0.1	3.3± 0.15	7.4± 0.05	8.2± 0.05	10.6± 0.05	10.6± 0.05
R9	2.5 ±0.1	4.7± 0.05	7.5 ±0.05	9.5± 0.05	12.6± 0.05	12.6± 0.05

4.5 In Vitro drug release studies

For the first two hours of the in vitro drug release investigations, a 1.2 pH HCl buffer solution was used. Then, the studies were continued in a 7.4 pH phosphate buffer solution. UV spectrophotometric measurements of the drug concentration were made at 313 nm. Up to 14 hours were spent on the studies.

The graphs were created by plotting the cumulative % drug release vs time, and they are displayed in Figure 7, respectively. After 14 hours, it was discovered that the drug release observed in formulation R9 was 98.9%. After 12 hours, it was discovered that the formulations R3 and R8 had cumulative % drug releases of 98.3% and 97.9%, respectively. After 11 hours, it was discovered that formulations R6 and R2 had cumulative % drug releases of 95.8% and 95.2%, respectively. After 10 hours,

formulation R5 cumulative % drug release was found to be 94.8%, respectively. After 9 hours, it was discovered that formulations R1 and R7 had cumulative % drug releases of 94.6% and 87.3%, respectively.

After 8 hours, it was discovered that formulation R4 had a cumulative % drug release of 93.5%. Because SCMC and HPMC both have high gelling and swelling abilities, the observed results showed that the formulations containing sodium alginate had the highest percentage of drug release characteristics. These are the parameters that are primarily involved in delaying the release of drugs from the formulations for 12 to 14 hours. R9 demonstrated the slowest rate of release out of all formulations and had the desired controlled release properties. Figure 7 displays the comparison findings for all formulations.

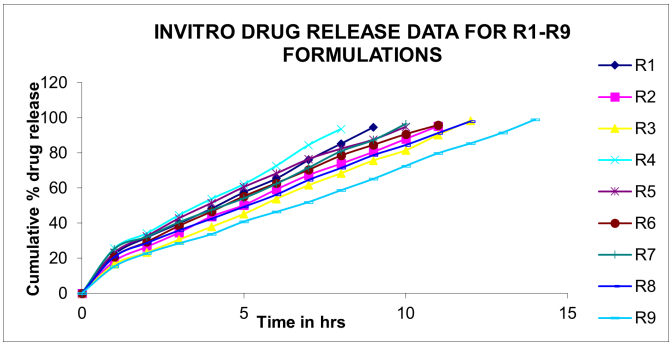

Fig 7. In vitro drug release data for R1-R9 formulations

4.6 Water uptake studies

According to the observations of water uptake studies R9 and R3 had the best water uptake out of all formulations, which can be attributed to the high swelling capacity of HPMC and SCMC. The increasing order of formulation was found in order of R9>R3>R8>R6>R7>R2>R1>R5>R4 (i.e.) 12.6±0.05, 10.7±0.05, 10.6±0.05, 9.6±0.05, 9.6±0.05, 8.2±0.05, 7.6±0.05, 7.3±0.11, 6.6±0.05 due to high water absorbing ability of HPMC and SCMC, hence the formulation containing HPMC and SCMC have high water uptake property than other formulations.

Table 6. Water uptake data for all formulations

Formulation code	Time in mins					
	60	**120**	**180**	**240**	**300**	**360**
R1	2.2±0.05	3.7± 0.1	5.6± 0.1	6.6 0.05	8.3± 0.05	8.5± 0.05
R2	3.3±0.05	4.5 ±0.05	5.4± 0.05	7.2± 0.05	8.6± 0.05	9± 0.05
R3	3.7 ±0.11	5.3± 0.05	7.3± 0.11	8.3± 0.1	11.8± 0.57	11.8± 0.57
R4	1.6± 0.15	3.6± 0.15	4.4± 0.05	5.3± 0.05	7.6± 0.05	7.6± 0.05
R5	2.3± 0.1	4.5± 0.15	5.8± 0.05	6.4± 0.05	8.3± 0.11	8.3± 0.11
R6	2.7± 0.1	5.6± 0.1	7.6± 0.15	8.5± 0.05	10.6± 0.05	10.6± 0.05
R7	2.1± 0	3.7± 0.1	6.4± 0.11	10.5±0.05	10.5± 0.05	10.5± 0.05
R8	2.5± 0.1	4.3± 0.15	8.6± 0.05	9.2± 0.05	11.6± 0.05	11.6± 0.05
R9	3.5 ±0.1	5.6± 0.05	8.5± 0.05	10.5±0.05	13.6 0.05	13.6± 0.05

4.7 SEM analysis

The SEM reports obtained showed good spherical shape and also surface morphological characters. The ionic gelation process was used to create the ranitidine hydrochloride hydrogel, which is ideal for further formulations. The solvent and polymers that were selected produced more hydrogels as a proportion of the total yield. FTIR investigations demonstrate that the polymers such as sodium alginate, HPMC K100, SCMC, and carbopol used for the creation of hydrogels do not significantly interact with drugs. The physicochemical tests that were conducted on all of the formulations produced satisfactory results. All of the formulations exhibit a regulated release pattern of the drug up to 14 hours according to the in vitro drug release experiments. In-vitro release and in vitro mucoadhesion showed good connection and repeatable findings. Ranitidine hydrochloride may

therefore be a good and appropriate candidate for usage in the creation of hydrogels and for pharmaceutical purposes.

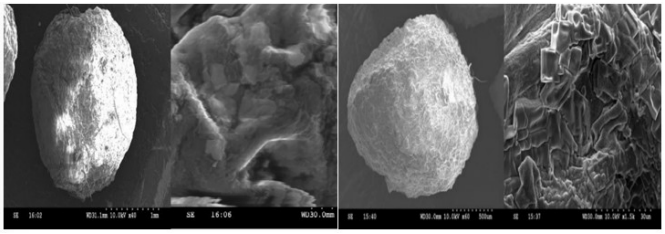

Fig 8. SEM Photograph of R3 & R6 formulation

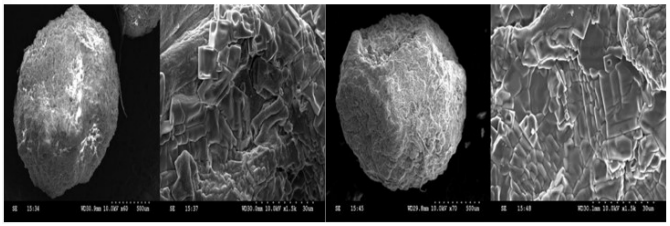

Fig 9. SEM Photograph of R8 & R9 formulation

5 Conclusion

To create the Ranitidine hydrochloride hydrogel beads, using sodium alginate as the primary polymer and secondary polymers such as HPMC K100, sodium carboxy methyl cellulose, and Carbopol. Generally, one gelling agent is used for the formulation of hydrogels but in the present research combination of polymers is used for best results. The solvent and polymers were selected based on the economic aspects and also the availability to produce more hydrogels as a proportion of the total yield. There are several methods such as chemical cross-linking to free radical polymerization techniques are used for the synthesis of hydrogels among them ionic gelation technique is economical, simple, and reproducible in nature. FTIR investigations demonstrate that the polymer used to make sodium alginate, HPMC K100, SCMC, and carbopol for the creation of hydrogels does not significantly interact with drugs. The physicochemical tests that were conducted on all of the formulations produced satisfactory results. All of the formulations exhibit a regulated release pattern of the drug for up to 14 hours according to the in vitro drug release experiments. In-vitro release and in-vitro mucoadhesion showed good connection and repeatable findings. Ranitidine hydrochloride may therefore be a good and appropriate candidate for usage in the creation of hydrogels and for site-specific delivery applications. It is observed that pharmaceutical applications of hydrogel-based dosage forms can provide controlled delivery of active ingredients along with site-specific applications. The application of innovative technologies can find new prospects in the replacement of conventional methods for the development of potentially effective site-specific controlled-release dosage forms by using biodegradable polymers in the pharmaceutical field. In spite of the multiple benefits provided by hydrogels in biomedical fields, and specific advantages in pharmaceutical applications they can be utilized for the development of bio-adhesive formulations by choosing polymers for specific applications. Applications of nanotechnology in the development of bio-adhesive hydrogels provide the advantage of adhesive properties in addition to multi-functional delivery applications. A nanotechnological approach in the development of hydrogel delivery systems can enhance prospects in delivery applications for site-specific treatment of diseases with the additional benefit of a longer duration of drug release. Yet there are a few barriers and challenges existing with hydrogels such as they cannot provide long-term adhesive properties, their structured research, and advancements are expected in the development of long-term bio adhesive hydrogel delivery systems.

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